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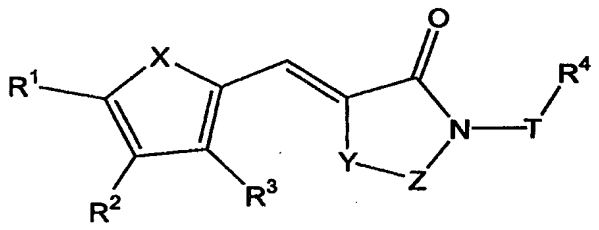

(1)

(57) Abstract

The present invention provides compounds of formula (1), where X is O, S, or $-CR^5=CR^6-$; Y is O, S, NR^7, or CH_2, Z is CH_2, C=O, or C=S, T is $(CH_2)_n$, NR^8, or $N(R^9)CO$; R^1, R^2, R^3, R^5, and R^6 are independently selected from the group consisting of hydrogen, heteroatoms, substituted or unsubstituted cycloalkyl, aryl, and heterocyclyl groups; R^4 is selected from the list consisting of hydrogen, substituted or unsubstituted alkyl, cycloalkyl, aryl, heterocyclyl, or carboxamide groups; R^7 is hydrogen or a substituted or unsubstituted alkyl group; R^8 and R^9 are independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, cycloalkyl, aryl, and heterocyclyl groups. R^4 and R^8 may also form part of a ring; and n is 0–6; and the pharmaceutically acceptable salts and prodrugs thereof. The present invention also provides compositions containing a compound of formula (1) and a pharmaceutically acceptable carrier and methods of inhibiting cellular proliferation by administering a compound of formula (1) to a host in need.

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Compounds That Inhibit The Binding Of Vascular Endothelial Growth Factor To Its Receptors

Field of the Invention

The present invention is directed to compounds that inhibit the binding of endothelial growth factor to its receptors and/or prevent receptor signal transduction.

Background of the Invention

Angiogenesis, the sprouting of new blood vessels from pre-existing vessels, depends on a delicate balance of local physical and chemical stimuli acting spatially and temporally on the vascular endothelium, the innermost lining of all blood vessels. It is now well-documented that angiogenesis, as well as vasculogenesis, the *in situ* development of blood vessels from differentiating endothelial cells (ECs), is regulated by a diverse repertoire of growth stimulators and inhibitors. At least 20 different angiogenic factors have been identified during the past decade (Fan T-PD, Jagger R, Bicknell R. Controlling the vasculature: angiogenesis, anti-angiogenesis and vascular targeting of gene therapy. Trends Pharmacol Sci 1995;16: 57-66). Certain angiogenic factors (e.g., acidic and basic fibroblast growth factor) act as direct mitogens or chemoattractants for ECs, while others (e.g., tumor necrosis factor-a, transforming growth factor-b) act indirectly by first recruiting inflammatory cells which then subsequently release ECs mitogens. In 1983, Dvorak and colleagues first described an unidentified tumor-derived vascular permeability factor which was a potent stimulus (50,000 times greater than histamine on a molar basis) for increasing blood vessel permeability and promoting fluid accumulation, and named this factor vascular permeability factor (VPF) (Senger DL, Galli SJ, Dvorak AM, Peruzzi VCA, Harvey VS, Dvorak HF. Tumor cells secrete a vascular permeability factor that promotes

accumulation of ascites fluid. Science 1983;219:983-985. Senger DR, Perruzzi CA, Feder J, Dvorak HF. A highly conserved vascular permeability factor secreted by a variety of human and rodent tumor cell lines. Cancer Res 1986;46:5629-5632). Subsequently, Connolly et al. found VPF to be a potent, selective mitogen for ECs, thus raising the possibility that VPF contributed to tumor cell-stimulated angiogenesis (Connolly DT, Olander JV, Heuvelman D, et al. Human vascular permeability factor: Isolation from U937 cells. J Biol Chem 1989;264: 20017-20024). At the same time, proteins referred to as vascular endothelial growth factor (VEGF; Ferrara N, Henzel WJ. Pituitary follicular cells secrete a novel heparin-binding growth factor specific for vascular endothelial cells, Biochem Biophys Res Commun 1989;161:851-858), vasculotropin (Plouët Schilling J, Gospodarowicz, D. Isolation and characterization of a newly identified endothelial cell mitogen by AtT-20 cells. EMBO J 1989;8:3801-3806) and glioma-derived vascular EC growth factor (GD-ECGF; Conn G, Sodermann DD, Schaeffer M-T, Wile M, Hatcher VB, Thomas KA. Purification of a glycoprotein vascular endothelial cell mitogen from a rat glioma-derived cell line. Proc Natl Acad Sci USA 1990;87:1323-1327) were isolated that exhibited functional and structural properties similar to VPF (Senger DL, Galli SJ, Dvorak AM, Peruzzi VCA, Harvey VS, Dvorak HF. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. Science 1983;219:983-985). Molecular cloning of the human, bovine and rat cDNAs for VPF (Connolly DT, Olander JV, Heuvelman D, et al. Human vascular permeability factor: Isolation from U937 cells. J Biol Chem 1989;264: 20017-20024), VEGF (Leung DW, Cachianes G, Kuang W-J, Goeddel DV, Ferrara N. Vascular endothelial growth factor is a secreted angiogenic mitogen. Science 1989;246:1306-1309) and GD-ECGF (Conn G, Bayne ML, Soderman DD, et al. Amino acid and cDNA sequences of a vascular endothelial cell mitogen that is homologous to platelet-derived growth factor. Proc Natl Acad Sci USA 1990;87: 2628-2632) have

demonstrated that these proteins are encoded by the same gene. Of the angiogenic factors described to date, VEGF is believed to be the most EC specific mitogen.

Vascular endothelial cell growth factor is a member of the heparin-binding family of growth factors which also includes platelet-derived growth factor (PDGF), the fibroblast growth factor family (FGF) (Burgess WH, Maciag T. The heparin-binding (fibroblast) growth factor family of proteins. Ann Rev Biochem 1989;58:575-606), and heparin-binding epidermal growth factor (Thompson SA, Higashiyama S, Wood K, et al. Characterization of sequences within heparin-binding EGF-like growth factor that mediate interaction with heparin. J Biol Chem 1994;269:2541-2549). The biologically active, native protein exists as a disulfide-bonded homodimer of 34-42 kDa molecular weight suggesting that multiple isoforms can be processed. This polypeptide growth factor is heat- and acid-stabile, exhibits a basic pH (8.5) and is glycosylated at Asn-74. Molecular cloning studies have documented the existence of a single human VEGF gene which is organized into 8 exons (Tischer E, Mitchell R, Hartman T, et al. The human gene for vascular endothelial growth factor: Multiple protein forms are encoded through alternative exon splicing. J Biol Chem 1991;266:11947-11954).

Vascular endothelial growth is a product of several different tumor cell types, including glioblastomas, sarcomas, carcinomas and histiocytic lymphomas (Senger DL, Galli SJ, Dvorak AM, Peruzzi VCA, Harvey VS, Dvorak HF. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. Science 1983;219:983-985. Senger DR, Perruzzi CA, Feder J, Dvorak HF. A highly conserved vascular permeability factor secreted by a variety of human and rodent tumor cell lines. Cancer Res 1986;46:5629-5632). Since these are tumor-derived cell lines, VEGF has been postulated to play roles in mediating tumor-associated angiogenesis and the abnormal increase in capillary

permeability seen in tumor vessels. Subsequently, VEGF has been isolated or detected in several normal tissues, including lung, kidney, liver, brain, adrenal gland, and heart, as well as different cell types using immunohistochemical and *in situ* hybridization techniques. In general, VEGF in normal tissues is localized to cells which reside in areas of high blood vessel permeability, such as the liver (hepatocytes), lungs (alveolar cells) and kidneys (glomeruli and tubules) (Monacci WT, Merrill MJ, Oldfield EH. Expression of vascular permeability factor/vascular endothelial growth factor in normal rat tissues. Am J Physiol 1993;264:C995-C1002. Senger DR Van De Water L, Brown LF, et al. Vascular permeability factor (VPF,VEGF) in tumor biology. Cancer Metastasis Rev 1993;12:303-324. Jakeman LB, Winer J, Bennett GL, Altar CA, Ferrara N. Binding sites for vascular endothelial growth factor are localized on endothelial cells in adult rat tissues. J Clin Invest 1992;89:244-253. Berse B, Brown LF, Van De Water L, Dvorak HF, Senger DR. Vascular permeability factor (vascular endothelial growth factor) gene is expressed differentially in normal tissues, macrophages, and tumors. Mol Biol Cell 1992;3:211-220), and in areas where EC turnover might be expected to be higher than normal, as in the cardiac myocytes near the valves of the heart (Jakeman LB, Winer J, Bennett GL, Altar CA, Ferrara N. Binding sites for vascular endothelial growth factor are localized on endothelial cells in adult rat tissues. J Clin Invest 1992;89:244-253).

In general, it has been known for some time that angiogenesis occurs in hypoxic tissues (Colville-Nash PR, and DL Scott. Angiogenesis and rheumatoid arthritis: pathological and therapeutic implications. Ann Rheum Disease 1992;51:919-925). Thus, most interesting and perhaps clinically relevant, is the observation that VEGF mRNA levels can be up-regulated in numerous cell types (Aiello LP, Northup JM, Keyt BA, Takagi H, Iwamoto MA. Hypoxic regulation of vascular endothelial growth factor in retinal cells. Arch Ophthalmol 1995;113:1538-1544. Namiki A, Brogi E,

Kearney M, et al. Hypoxia induces vascular endothelial growth factor in cultured human endothelial cells. J Biol Chem 1995;270:31189-31195. Minchenko A, Bauer T, Salceda S, Caro J. Hypoxic stimulation of vascular endothelial growth factor expression *in vitro* and *in vivo*. Lab Invest 1994;71:374-379) and animals (Pe'er J, Shweiki D, Itin A, Hemo I, Gnessin H, Keshet E. Hypoxia-induced expression of vascular endothelial growth factor by retinal cells is a common factor in neovascularizing ocular diseases. Lab Invest 1995;72:638-645. Tuder RM, Flook BE, Voelkel NF. Increased gene expression for VEGF and the VEGF receptors kdr/Flk and flt in lungs exposed to acute or to chronic hypoxia. J Clin Invest 1995;95:1798-1807. Ladoux A, Frelin C. Hypoxia is a strong inducer of vascular endothelial growth factor mRNA expression in the heart. Biochem Biophys Res Commun 1993;195:1005-1010) in response to hypoxia. Although PDGF-BB and TGF-b can increase VEGF and FGF2 mRNA levels in cells, only hypoxia specifically induces VEGF mRNA levels (Brogi E, Wu T, Namiki A, Isner JM. Indirect angiogenic cytokines upregulate VEGF and bFGF gene expression in vascular smooth muscle cells, whereas hypoxia upregulates VEGF expression only. Circulation 1994;90(2):649-652). Treatment with a monoclonal antibody directed against VEGF reduces the vascular density and inhibits the growth of several human tumors in nude mice without affecting the growth rate of tumor cells *in vitro* (Kim KJ, Li B, Winer J, Armanini M, et al. Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth *in vivo*. Nature 1993;362:841-844). Interestingly, hypoxia has also been shown to be a strong stimulus to induce VEGF mRNA levels in retinal pigment epithelial cells (Aiello LP, Northup JM, Keyt BA, Takagi H, Iwamoto MA. Hypoxic regulation of vascular endothelial growth factor in retinal cells. Arch Ophthalmol 1995;113:1538-1544.) and increase the number of VEGF receptors in retinal endothelial cells (Thieme H, Aiello LP, Takagi H, Ferrara N, King GL. Comparative analysis of vascular endothelial growth factor receptors on retinal and aortic vascular

endothelial cells. Diabetes 1995; 44:98-103). There are now numerous studies showing that increased ocular expression of VEGF mRNA and protein levels is closely correlated with neovascularization in patients with proliferative diabetic retinopathy (Malecaze F, Clamens S, Simorre-Pinatel V, et al. Detection of vascular endothelial growth factor messenger RNA and vascular endothelial growth factor-like activity in proliferative diabetic retinopathy. Arch Opthamol 1994;112:1476-1482. Adamis AP, Miller JW, Bernal MT, et al. Increased vascular endothelial growth factor levels in the vitreous of eyes with proliferative diabetic retinopathy. Am. J. Opthamol. 1994;118:445-450. Aiello LP, Avery RL, Arrigg PG, et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med 1994;331:1480-1487) and in different animal models of ischemia-induced retinal neovascularization, including retinal vein occlusion and retinopathy of prematurity (Miller JW, Adamis AP, Shima DT, et al. Vascular endothelial growth factor/vascular permeability factor is temporally and spatially correlated with ocular angiogenesis in a primate model. Am J Pathol 1994;145:574-584. Pierce EA, Avery RL, Foley ED, Aiello LP, Smith LEH. Vascular endothelial growth factor/vascular permeability factor expression in a mouse model of retinal neovascularization. Proc. Natl. Acad. Sci. USA 1995;92:905-909). Application of anti-VEGF antibodies following retinal vein occlusion prevented iris neovascularization in nonhuman primates (Adamis AP, Shima DT, Tolentino MJ, et al. Inhibition of vascular endothelial growth factor prevents retinal ischemia-associated iris neovascularization in a nonhuman primate. Arch Opthamol 1996;114:66-71). Furthermore, Aiello et al. (Aiello LP, Pierce EA, Foley ED, et al. Suppression of retinal neovascularization *in vivo* by inhibition of vascular endothelial growth factor (VEGF) using soluble VEGF-receptor chimeric proteins. Proc Natl Acad Sci USA 1995;92:10457-10461) demonstrated that a soluble VEGF receptor chimeric protein was capable of suppressing neovascularization in a mouse model of retinopathy of prematurity.

Cellular hyperplasia, hypoxia, angiogenesis, and fluid accumulation are also hallmark changes that are correlated closely with the development of the destructive synovial pannus in rheumatoid arthritis (Colville-Nash PR, and DL Scott. Angiogenesis and rheumatoid arthritis: pathological and therapeutic implications. Ann Rheum Disease 1992;51:919-925). Not surprisingly, increased levels of VEGF have been detected in the synovial fluid of patients with rheumatoid arthritis (Fava RA, Olsen NJ, Spencer-Green G, et al. Vascular permeability factor/ endothelial growth factor (VPF/VEGF): Accumulation and expression in human synovial fluids and rheumatoid synovial tissue. J Exp Med 1994;180:341-346. Koch A, Harlow L, Haines G, et al. Vascular endothelial growth factor. A cytokine modulating endothelial function in rheumatoid arthritis. J Immunol 1994;152:4149-4156). Thus, increases in VEGF expression may be a common mechanism underlying diverse, yet inter-related pathologies such as tumor growth, retinal neovascularization and rheumatoid arthritis where tissue hypoxia is a central component.

Numerous studies have described specific binding sites for VEGF on cultured ECs *in vitro* (Olander JV, Connolly DT, DeLarco JE. Specific binding of vascular permeability factor to endothelial cells. Biochem Biophys Res Commun 1991;175:68-76. Bikfalvi A., Sauzeau C, Moukadiri H, et al. Interaction of vasculotropin/vascular endothelial cell growth factor with human umbilical vein endothelial cells: Binding, internalization, degradation and biological effects. J Cell Physiol. 1991;149:50-59). Previous studies had shown that these binding sites exhibited high affinity (16-35 pM) and low capacity (2-7 fmol/mg protein) for [^{125}I]VEGF. The first VEGF receptor to be cloned was the human *flt* or Flt-1 receptor (*fms*-like tyrosine kinase) (Satoh H, Yoshida MC, Matsushime H, Shibuya M, Sasaki M. Regional localization on the human c-*ros*-1 on 6q22 and *flt* on 13q12. Jpn J Cancer Res 1987;78:772-775. Shibuya M, Yamaguchi S, Yamane A, et al. Nucleotide sequence and

expression of a novel human receptor-type tyrosine kinase gene (*flt*) closely related to the *fms* family. Oncogene 1990;8:519-524. DeVries C, Escobedo JA, Ueno H, Houck K, Ferrara N, Williams, LT. The *fms*-like tyrosine kinase, a receptor for vascular endothelial growth factor. Science 1992;255:989-991). More recently, a second high-affinity, human VEGF receptor, KDR (kinase insert domain-containing receptor) (Terman BI, Dougher-Vermazen M, Carrion ME, et al. Identification of the KDR tyrosine kinase as a receptor for vascular endothelial cell growth factor. Biochem Biophys Res Commun 1992;187:1579-1586) has been cloned and shown to be homologous to mouse Flk-1 (fetal liver kinase-1) (Matthews W, Jordan CT, Gavin M, Jenkins NA, Copeland NG, Lemischka IR. A receptor tyrosine kinase cDNA isolated from a population of enriched primitive hematopoietic cells and exhibiting close genetic linkage to c-*kit*. Proc Natl Acad Sci USA 1991;88:9026-9030. Millauer B, Wizigmann-Voos S, Schnurch H, et al. High affinity VEGF Binding and developmental expression suggest Flk-1 as a major regulator of vasculogenesis and angiogenesis. Cell 1993;72:835-846) or NYK/FLK-1 (neuroepithelial tyrosine kinase) (Oelrichs RB, Reid HH, Bernard O, Ziemiecki A, Wilks AF. NYK/FLK-1: A putative receptor protein tyrosine kinase isolated from E10 embryonic neuroepithelium is expressed in endothelial cells of the developing embryo. Oncogene 1993;8:11-18) and to rat TKr-C (Sarzani R, Arnaldi G, DePirro R, Moretti P, Schiaffino S, Rappelli A. A novel endothelial tyrosine kinase cDNA homologous to platelet-derived growth factor receptor cDNA. Biochem Biophys Res Comm 1992;186:706-714). Flt-1 and KDR exhibit an overall identity of 46%. Both receptor isoforms were found to be homologous to members of the class III family of receptor tyrosine kinases (RTKs). Class III RTKs are characterized by receptors that exhibit an extracellular ligand binding region which is composed of five immunoglobulin (IgG)-like domains, a single transmembrane-spanning domain and an intracellular tyrosine kinase domain. However, both Flt-1 and KDR have seven IgG domains in their

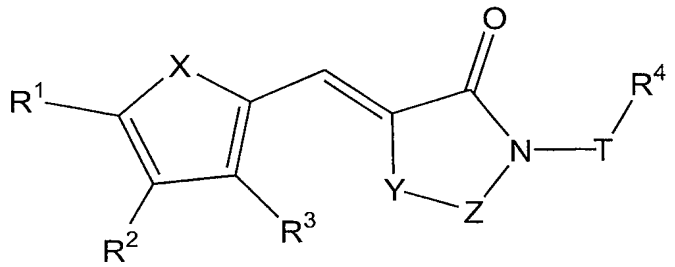
extracellular region. Furthermore, unlike the epidermal growth factor (Class I) and insulin (Class II) RTKs, the intracellular tyrosine kinase domain of class III RTKs is interrupted by a large non-kinase area called a "kinase insert" region. Upon ligand activation, receptor subunits are believed to dimerize and undergo transautophosphorylation at specific tyrosine residues within different areas of the cytoplasmic region. The purpose of these phosphorylated tyrosine residues is to present the appropriate binding sites for certain down-stream signaling proteins. With the discovery of other Flt-1-like RTKs, the *flt* receptor family has recently been designated a separate class (Class VII) of RTKs (Yarden Y, Ullrich A. Growth factor receptor tyrosine kinases. Ann Rev Biochem 1988;57:443-478). Early studies demonstrated that VEGF was a specific, potent mitogen for numerous vascular EC types, including bovine adrenal cortex, cerebral cortex, fetal and adult aorta, and human umbilical vein (EC_{50}=2-3 pM). This growth factor did not exhibit mitogenic effects on corneal ECs, vascular smooth muscle cells, BHK-21 fibroblasts, keratinocytes, human sarcoma cells, or lens epithelial cells (Gospodarowicz D, Ferrara N, Schweigerer L, Neufeld G. Structural characterization and biological functions of fibroblast growth factor. Endocr Rev 1987;8:95-114. Connolly DT, Heuvelman DM, Nelson R, et al. Tumor vascular permeability factor stimulates endothelial cell growth and angiogenesis. J. Clin. Invest. 1989;84: 1470-1478). *In situ* hybridization has been used to demonstrate that VEGF receptors are present in the early yolk sac and hemangioblasts within the yolk sac (Jakeman LB, Armanini M, Phillips HS, Ferrara N. Developmental expression of binding sites and messenger ribonucleic acid for vascular endothelial growth factor suggests a role for this protein in vasculogenesis and angiogenesis. Endocrinology 1993;133(2):848-859). Using homologous recombination of emrbyonic stem cells to produce KDR-deficient mice, Shalaby et al. (Shalaby F, Rossant J, Yamaguchi TP, et al. Failure of blood-island formation and vasculogenesis in FLK-1-deficient mice. Nature (Lond.) 1995;376:62-66)

showed that embryos died *in utero* as a result of defect in the development of haematopoietic and endothelial cells. These results suggest that the Flk-1/KDR receptor is essential for yolk-sac angioblast formation and vasculogenesis very early in embryonic development. Likewise, Fong et al (Fong G-H, Rossant J, Gertsenstein M, Breitman ML. Role of the Flt-1 receptor tyrosine kinase in regulating the assembly of vascular endothelium. Nature (Lond.) 1995;376:66-70) produced FLT-1 deficient mice and showed that these mice also died *in utero* although at a slightly later gestational stage then the KDR-deficient mice. However, in contrast with the flk-1-deficient mice, the FLT-1-deficient mice formed ECs in both the embryonic and extra-embryonic regions, but were assembled into abnormal vascular channels. These results suggest that FLT-1 may play a role in normal EC organization during vascular development. Taken together, these observations provide evidence that VEGF plays a fundamental role in early vasculogenesis.

Therefore, compounds capable of inhibiting the binding of VEGF to its receptors and/or preventing receptor signal transduction may be expected to play a role in the treatment of certain diabetic complications, tumor growth, retinal neovascularization, rheumatoid arthritis, and other disease settings mediated by vascular proliferation.

Summary of the Invention

The present invention provides compounds of the formula:



1

where:

X is O, S, or $-CR^5=CR^6-$;
Y is O, S, NR^7, or CH_2,
Z is CH_2, C=O, or C=S,
T is $(CH_2)_n$, NR^8, or $N(R^9)CO$;
R^1, R^2, R^3, R^5, and R^6 are independently selected from the group consisting of hydrogen, heteroatoms, substituted or unsubstituted cycloalkyl, aryl, and heterocyclyl groups;
R^4 is selected from the list consisting of hydrogen, substituted or unsubstituted alkyl, cycloalkyl, aryl, heterocyclyl, or carboxamide groups;
R^7 is hydrogen or a substituted or unsubstituted alkyl group;
R^8 and R^9 are independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, cycloalkyl, aryl, and heterocyclyl groups. R^4 and R^8 may also form part of a ring; and
n is 0-6;
and the pharmaceutically acceptable salts and prodrugs thereof.

Particularly preferred compounds are those where:

X is O;
Y is S and Z is C=S;
Y is NH and Z is C=O;
Y is CH_2 and Z is C=O;
T is $(CH_2)_n$;
n is 0-3;
R^1 is independently selected from the group consisting of substituted or unsubstituted aryl, and heterocyclyl groups;
R^2 and R^3 are hydrogen; and
R^4 is selected from the group consisting of substituted or unsubstituted aryl, heterocyclyl, and carboxamide groups;
and the pharmaceutically acceptable salts and prodrugs thereof.

Particularly preferred compounds include:

Compound #	Name
1	4-{5-[(3-benzyl-4-oxo-2-thioxo-1,3-thiazolan-5-ylidene)methyl]-2-furyl}benzenesulfonamide
2	3-{[5-(4-chlorophenyl)-2-furyl]methylidene}-1-(4-morpholinophenyl)dihydro-1H-pyrrole-2,5-dione
3	1-(4-morpholinophenyl)-3-({5-[2-nitro-4-(trifluoromethyl)phenyl]-2-furyl}methylidene)dihydro-1H-pyrrole-2,5-dione
4	1-benzyl-3-[(5-phenyl-2-furyl)methylidene]-2-pyrrolidinone
5	3-benzyl-5-[(5-phenyl-2-furyl)methylidene]-1,3-thiazolan-4-one
6	5-{[5-(4-chlorophenyl)-2-furyl]methylidene}-3-[4-(4-methylpiperazino)phenyl]-2-thioxo-1,3-thiazolan-4-one
7	4-[4-(5-{[5-(4-chlorophenyl)-2-furyl]methylidene}-4-oxo-2-thioxo-1,3-thiazolan-3-yl)phenyl]butanoicacid
8	4-(5-{[3-(1,3-benzodioxol-5-ylmethyl)-4-oxo-2-thioxo-1,3-thiazolan-5-ylidene]methyl}-2-furyl)benzenesulfonamide
9	5-{ [5-(4-bromophenyl)-2-furyl]methylidene}-3-(3-chloro-4-morpholinophenyl)-2-thioxo-1,3-thiazolan-4-one
10	4-[5-({3-[4-(dimethylamino)benzyl]-4-oxo-2-thioxo-1,3-thiazolan-5-ylidene}methyl)-2-furyl]benzenesulfonamide
11	4-[5-({3-[(6-methyl-1,3-benzodioxol-5-yl)methyl]-4-oxo-2-thioxo-1,3-thiazolan-5-ylidene}methyl)-2-furyl]benzenesulfonamide
12	4-(5-{[3-(3-bromobenzyl)-4-oxo-2-thioxo-1,3-thiazolan-5-ylidene]methyl}-2-furyl)benzenesulfonamide
13	2-amino-N-(4-{5-[(3-benzyl-4-oxo-2-thioxo-1,3-thiazolan-5-ylidene)methyl]-2-furyl}phenyl)acetamide
14	2-[2-(2-aminoethoxy)ethoxy]-5-(5-{[5-(4-bromophenyl)-2-furyl]methylidene}-4-oxo-2-thioxo-1,3-thiazolan-3-yl)benzoic acid
15	4-{5-[(3-benzyl-4-oxo-2-thioxo-1,3-thiazolan-5-ylidene)methyl]-2-furyl}-N-(6-hydroxyhexyl)benzenesulfonamide
16	4-[5-({1-[(6-methyl-1,3-benzodioxol-5-yl)methyl]-2,5-dioxo-3-pyrrolidinylidene}methyl)-2-furyl]benzenesulfonamide
17	3-[[1,1'-biphenyl]-4-ylmethylidene]-1-[(6-methyl-1,3-benzodioxol-5-yl)methyl]dihydro-1H-pyrrole-2,5-dione
18	1-[(6-methyl-1,3-benzodioxol-5-yl)methyl]-3-{[4-(1-pyrrolidinyl)phenyl]methylidene}dihydro-1H-pyrrole-2,5-dione
19	N-(4-{5-[(3-benzyl-4-oxo-2-thioxo-1,3-thiazolan-5-ylidene)methyl]-2-furyl}phenyl)-2-hydroxyacetamide
20	5-{[5-(4-bromophenyl)-2-furyl]methylidene}-3-[3-(4-methylpiperazino)-3-oxopropyl]-2-thioxo-1,3-thiazolan-4-one
21	N-(5-{[5-(4-bromophenyl)-2-furyl]methylidene}-4-oxo-2-thioxo-1,3-thiazolan-3-yl)benzamide
22	2-amino-N-{4-[5-({3-[(6-methyl-1,3-benzodioxol-5-yl)methyl]-4-oxo-2-thioxo-1,3-thiazolan-5-ylidene}methyl)-2-furyl]phenyl}acetamide
23	4-(5-{[3-(3-hydroxybenzyl)-4-oxo-2-thioxo-1,3-thiazolan-5-ylidene]methyl}-2-furyl)benzenesulfonamide
24	5-{[5-(4-bromophenyl)-2-furyl]methylidene}-3-(2-oxo-2-piperazinoethyl)-2-thioxo-1,3-thiazolan-4-one
25	3-{2-[4-(2-aminoacetyl)piperazino]-2-oxoethyl}-5-{[5-(4-bromophenyl)-2-furyl]methylidene}-2-thioxo-1,3-thiazolan-4-one
26	4-(5-{[3-(3-chlorobenzyl)-4-oxo-2-thioxo-1,3-thiazolan-5-ylidene]methyl}-2-furyl)benzenesulfonamide
27	4-(5-{[3-(3-iodobenzyl)-4-oxo-2-thioxo-1,3-thiazolan-5-ylidene]methyl}-2-furyl)benzenesulfonamide
28	5-{[5-(4-bromophenyl)-2-furyl]methylidene}-3-[3-(dimethylamino)phenyl]-2-thioxo-1,3-thiazolan-4-one
29	5-{5-[(5-{4-[2-(3-cyanophenoxy)ethoxy]phenyl}-2-furyl)methylidene]-4-oxo-2-thioxo-1,3-thiazolan-3-yl}-2-({2-[2-(2-methoxyethoxy)ethoxy]acetyl}amino)benzoic acid

30	2-amino-N-(4-{5-[(1-benzyl-2,5-dioxotetrahydro-4H-imidazol-4-ylidene)methyl]-2-furyl}phenyl)acetamide
31	5-(5-{5-(4-bromophenyl)-2-furyl]methylidene}-4-oxo-2-thioxo-1,3-thiazolan-3-yl)-2-(2-{2-[(tert-butoxycarbonyl)amino]ethoxy}ethoxy)benzoic acid
32	3-benzyl-5-({5-[4-(methoxymethoxy)phenyl]-2-furyl}methylidene)-2-thioxo-1,3-thiazolan-4-one
33	2-{[2-(5-{[5-(4-bromophenyl)-2-furyl]methylidene}-4-oxo-2-thioxo-1,3-thiazolan-3-yl)acetyl]amino}acetic acid
34	(2S)-5-{[amino(imino)methyl]amino}-2-{[2-(5-{[5-(4-bromophenyl)-2-furyl]methylidene}-4-oxo-2-thioxo-1,3-thiazolan-3-yl)acetyl]amino}pentanoic acid
35	4-[5-({3-[(6-nitro-1,3-benzodioxol-5-yl)methyl]-4-oxo-2-thioxo-1,3-thiazolan-5-ylidene}methyl)-2-furyl]benzenesulfonamide
36	2-(acetylamino)-5-(5-{[5-(3-hydroxyphenyl)-2-furyl]methylidene}-4-oxo-2-thioxo-1,3-thiazolan-3-yl)benzoic acid
37	3-benzyl-5-{[5-(3-hydroxyphenyl)-2-furyl]methylidene}-2-thioxo-1,3-thiazolan-4-one

The present invention also provides compositions containing a compound of formula 1 and a pharmaceutically acceptable carrier and methods of inhibiting cellular proliferation by administering a compound of formula 1 to a host in need.

Detailed Description of the Invention

As used herein, the term "aryl" means a carbocyclic aromatic group, as for example phenyl, naphthyl, indenyl, indanyl, anthracenyl, and the like.

As used herein, the term "alkyl" means straight or branched, saturated or unsaturated carbon chains having up to 10, preferably up to 6 and more preferably up to 4 carbon atoms.

As used herein, the term "cycloalkyl" means non-aromatic carbocylic groups for example cyclopropyl, cyclopentyl, cyclohexenyl, norbornyl, and the like.

The term "heterocyclyl" refers to an aromatic or non-aromatic cyclic group having one or more oxygen, nitrogen or sulfur atoms in the ring, as for example, furyl, thienyl, pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl,

indolinyl, benzo[b]furanyl, 2,3-dihydrobenzofuranyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzothiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, and phenoxizinyl, tetrahydrofuranosyl, tetrahydropyranosyl, piperidinyl, piperazinyl, and the like.

Suitable substituents for the aryl, alkyl, cycloalkyl, or heterocyclyl groups, when present, include carboxylic acids, alcohols, amines, amides, heteroatoms, or any combination of aryl, alkyl, cycloalkyl or heterocyclyl groups either attached directly, or *via* suitable linkers. The linkers are typically short chains of 1-3 atoms containing any combination of C, C=O, O, N, or S, S=O, SO_2, as for example ethers, amides, amines, ureas, sulfamides, sulfonamides, and the like.

In another aspect, the present invention provides a pharmaceutical composition comprising a compound of the present invention and a physiologically tolerable diluent.

The present invention includes one or more compounds of the present invention as described above formulated into compositions together with one or more non-toxic physiologically tolerable or acceptable diluents, carriers, adjuvants or vehicles that are collectively referred to herein as diluents, for parenteral injection, for oral administration in solid or liquid form, for rectal or topical administration, or the like.

The compositions can be administered to humans and animals either orally, rectally, parenterally (intravenous, by intramuscularly or subcutabeously), intracisternally, intravaginally, intraperitoneally, locally (powders, ointments or drops), or as a buccal or nasal spray.

The compositions can also be delivered through a catheter for local delivery at the site of vascular damage, via an intracoronary stent (a tubular device composed of a fine wire mesh), or via a biodegradable polymer. The compositions may also be complexed to ligands, such as antibodies, for targeted delivery of the compositions to the site of smooth muscle cell proliferation.

The compositions are, preferably, administered via parenteral delivery at the local site of smooth muscle cell proliferation. The parenteral delivery is, preferably, via catheter.

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or non-aqueous solutions, dispersions, suspensions or emulsions and sterile powders for reconstitution into steriale injectable solutions or dispersions. Examples of suitable aqueous and non-aqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

These compositions can also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

Dosage forms for topical administration of a conjugate of this invention include ointments, powders, sprays and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers or propellants as may be

required. Ophthalmic formulations, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

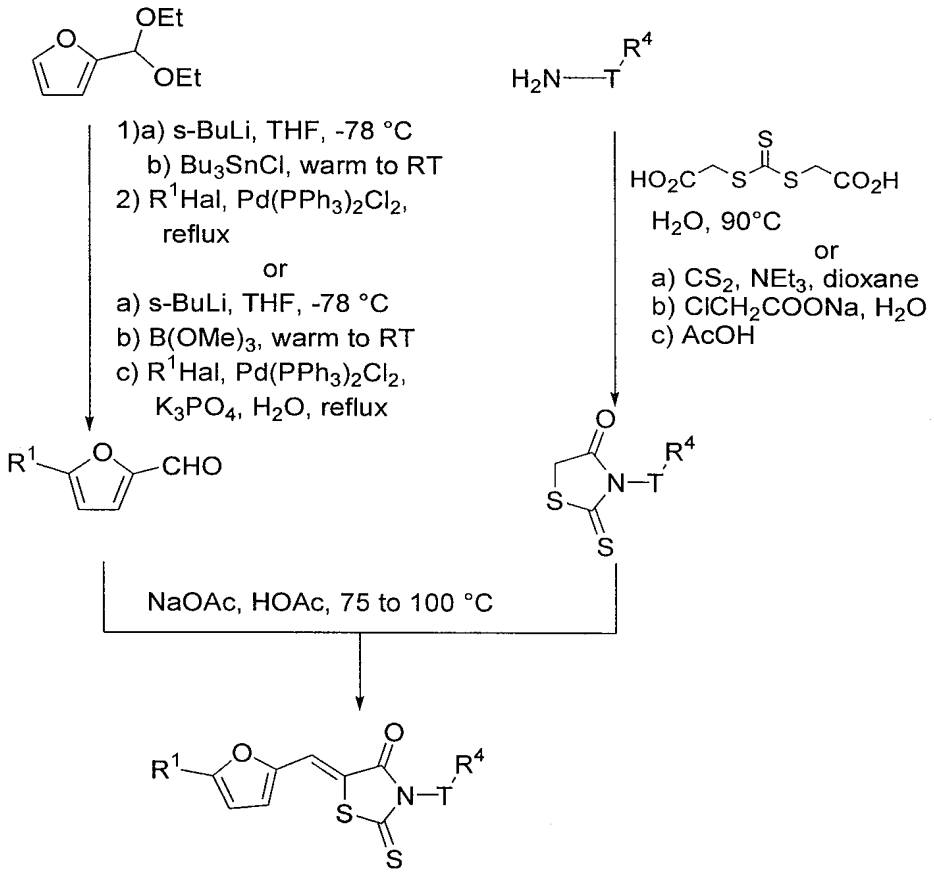
The agents can also be administered in the form of liposomes. As in known in the art, liposomes are generally derived form phospholipids or other lipid substances. Liposomes are formed by mono- or multilameller hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxid, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain stabilizers, preservatives, excipients, and the like in addition to the agent. The preferred lipids are phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic.

Methods of forming liposomes are known in the art. See, for example, Prescott, Ed., *Methods in Cell Biology*. Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

The present invention is further directed to a method of treating diseases or disorders that are characterized by excessive smooth muscle proliferation or diseases or disorders characterized by excessive neovascularization and permeability comprising administering an effective amount of a compound of the present invention to a patient in need of such treatment. An effective amount of a compound of the present invention will vary according to the desired therapeutic effect, the route of administration, the duration of treatment and other factors. The total daily dose of a compound of the present invention that is administered to a patient may be in single or divided dose(s). The specific dosage will vary depending upon a variety of factors including body weight, general health, sex, age, diet, time and route of administration, rates of absorption and excretion and the severity of the disease being treated.

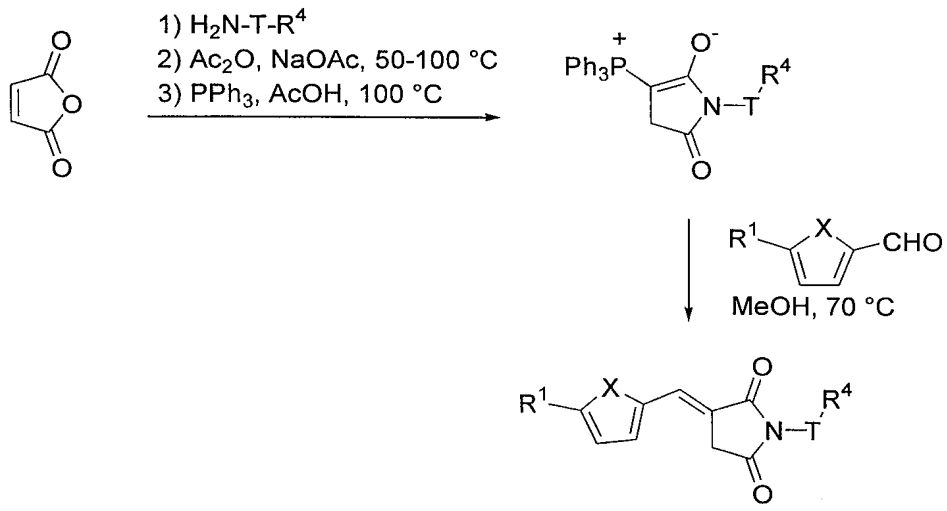
A preferred method of preparing representative compounds of the present invention when X is O, Y is S and Z is C=S is illustrated in the general synthetic scheme 1 below:

Scheme 1



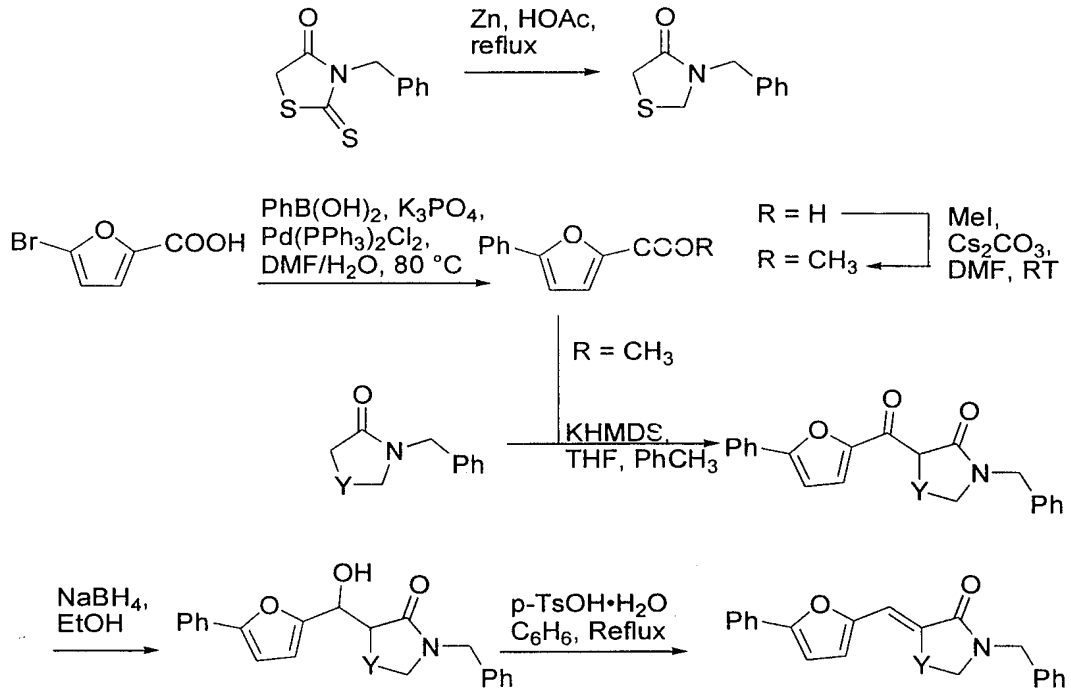
When Y is CH_2 and Z is C=O, a preferred method of preparing representative compounds is illustrated in the following scheme 2.

Scheme 2



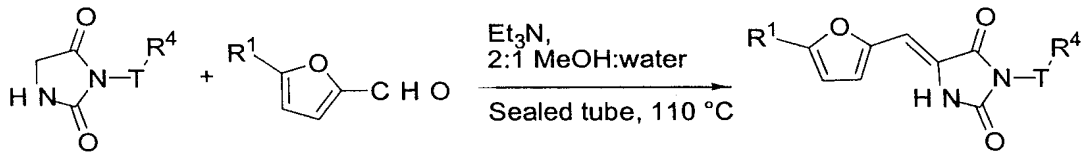
When X is O, Y is S or CH_2, and Z is CH_2, a preferred method of preparing representative compounds is illustrated in the following scheme 3.

Scheme 3



When X is O, Y is NH and Z is C=O, a preferred method of preparing representative compounds is illustrated in the following scheme 4.

Scheme 4



In general, the compounds described herein were prepared by the formation of an exocyclic double bond via a dehydrative addition-elimination reaction between an aldehyde or ester and the active methylene unit of a cyclic system. Representative examples of the cyclic systems are given in the appropriate sections. Representative examples of the synthesis of the aldehydes are given below:

Aldehyde Synthesis: General Procedures

Example 1: 5-(N-(N-*tert*-Butoxycarbonylglycine)-4-aminophenyl)-2-furaldehyde

To a solution of 0.43 ml furfural diethyl acetal (2.52 mmol) in 8.4 ml THF at -78 °C under nitrogen, 2.50 ml of a 1.3 M solution of sec-butyllithium in cyclohexane (3.28 mmol) was added dropwise by syringe. The resulting mixture was stirred at -78 °C for 2 hours and then 0.39 ml trimethylborate (3.44 mmol) was added by syringe. The solution was allowed to warm to room temperature and then stirred for 2 hours. At this point, 632 mg N-(N-*tert*-butoxycarbonylglycine)-4-iodoaniline (1.68 mmol) and a solution of 535 mg K_3PO_4 (2.52 mmol) in 3.2 ml water were added. The flask was fitted with a reflux condenser and the system was deoxygenated by transferring five times between vacuum and nitrogen. A catalytic amount of $Pd(PPh_3)_2Cl_2$ was added and the system was deoxygenated as before. The mixture was heated to reflux overnight, cooled to room temperature and diluted with EtOAc and water. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated under vacuum and the residue was purified by silica gel chromatography, eluting with 3:1 hexanes:EtOAc increasing to 1:1 hexanes:EtOAc to yield 650 mg of the diethyl acetal as a light yellow oil. This material was dissolved in 4 ml THF and 1 ml $CDCl_3$ and 1 drop water was added. The mixture was stirred for 15 minutes and concentrated under vacuum. The residue was dissolved in THF, diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$ and filtered and the filtrate was concentrated under vacuum to yield a light yellow

solid. This material was recrystallized from EtOAc with a small amount of THF to yield 307 mg 5-(N-(N-*tert*-butoxycarbonylglycine)-4-aminophenyl)-2-furaldehyde as light yellow crystals (53%). ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) δ 1.41 (s, 9H), 3.75 (d, J = 5.8 Hz, 2H), 7.03 (t, J = 5.8 Hz, 1H), 7.17 (d, J = 4.0 Hz, 1H), 7.63 (d, J = 4.0 Hz, 1H), 7.74 (d, J = 8.8 Hz, 2H), 7.83 (d, J = 8.8 Hz, 2H), 9.58 (s, 1H), 10.14 (br. s, 1H).

Example 2: 5-(4-Sulfamoylphenyl)-2-furaldehyde

To a solution of 1.69 ml furfural diethyl acetal (10.0 mmol) in 33 ml THF at -78 °C under nitrogen, 10 ml of a 1.3 M solution of sec-butyllithium in cyclohexane (13.0 mmol) was added dropwise by syringe. The resulting mixture was stirred at -78 °C for 2 hours and then 3.53 ml tributyltinchloride (13.0 mmol) was added by syringe. The resulting solution was allowed to gradually warm to room temperature and was then stirred at that temperature for 38 hours. To the resulting mixture, 14 ml of 2N HCl was added followed immediately with the addition of 200 ml of a 9:1 hexanes:EtOAc mixture. The mixture was washed with water, saturated aqueous $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$ and filtered and the filtrate was concentrated under vacuum to give a dark brown oil. This material was purified by silica gel chromatography, eluting with 19:1 hexanes:EtOAc to yield 3.17 g 5-tributylstannyl-2-furaldehyde as a light yellow oil (82%). This material was dissolved in 41 ml THF at room temperature under nitrogen and 1.77 g 4-bromobenzenesulfonamide (7.48 mmol) was added. The flask was fitted with a reflux condenser and the system was deoxygenated by transferring five times between vacuum and nitrogen. A catalytic amount of $Pd(PPh_3)_2Cl_2$ was added and the system was deoxygenated as before. The mixture was heated to reflux overnight, cooled to room temperature, adsorbed onto silica gel and then purified by silica gel chromatography, eluting with 1:1 hexanes:EtOAc increasing to EtOAc to yield 1.67 g light yellow solid. This material was further purified by recrystallization from hexanes/acetone to yield 1.03 g 5-(4-sulfamoylphenyl)-2-furaldehyde as yellow crystals (55%). ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) 7.43 (m, 3H),

7.68 (d, J = 4.0 Hz, 1H), 7.94 (d, J = 8.4 Hz, 2H), 8.06 (d, J = 8.4 Hz, 2H), 9.67 (s, 1H).

The preparation of the compounds of the present invention may be further illustrated by the following representative examples in which compounds are identified in the Table hereinabove:

Compounds of Scheme 1

Rhodanine Synthesis: General Procedures

Example 3: 3-(2-Methyl-4,5-methylenedioxybenzyl)rhodanine

To a solution of 374 mg 2-methyl-4,5-methylenedioxybenzylamine (2.54 mmol) and 0.39 ml triethylamine (2.79 mmol) in 4 ml dioxane at 0 °C, 153 µl carbondisulfide (2.54 mmol) was added by syringe. The reaction mixture was stirred at 0 °C for 5 minutes, warmed to room temperature and then stirred for 10 minutes. To the resulting mixture, a solution of 340 mg chloroacetic acid, sodium salt (2.92 mmol) in 5 ml water was added. The mixture was heated to 100 °C for 10 minutes then cooled to room temperature and 5 ml water and 5 ml of a 4:1 water:acetic acid mixture were added sequentially. The resulting mixture was stirred at room temperature overnight, 15 ml water was added and the mixture was filtered to collect the yellow solid which had formed, washing with saturated aqueous $NaHCO_3$ and water. The solid was taken up in 30 ml hot methanol to give a suspension which was cooled to room temperature and filtered, washing with cold methanol. The solid was dried under vacuum to give 321 mg 3-(2-methyl-4,5-methylenedioxybenzyl)rhodanine as a light yellow solid (47%). ^1H NMR (400 MHz, $CDCl_3$) 2.36 (s, 3H), 4.04 (s, 2H), 5.07 (s, 2H), 5.89 (s, 2H), 6.49 (s, 1H), 6.63 (s, 1H).

Example 4: 3-(3-Chloro-4-morpholinophenyl)rhodanine

To a solution of 0.50 g N-(4-amino-2-chlorophenyl)morpholine (2.35 mmol) in 3 ml water at room temperature, 0.56 g bis(carboxymethyl) trithiocarbonate (2.5 mmol) was added. The mixture was heated to 90 °C

overnight, cooled to room temperature and filtered, washing with water. The solid was dried under vacuum to give 0.58 g 3-(3-chloro-4-morpholinophenyl)rhodanine (76%). ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) 3.05 (t, J = 4.6 Hz, 4H), 3.77 (t, J = 4.6 Hz, 4H), 4.35 (s, 2H), 7.23 (dd, J = 8.6, 2.2 Hz, 1 H), 7.28 (d, J = 8.6 Hz, 1H), 7.40 (d, J = 2.2 Hz, 1H).

Coupling of aldehydes and rhodanines

Example 5: Compound 12

To a solution of 34.8 mg 3-(3-bromobenzyl)rhodanine (0.115 mmol) in 0.6 ml glacial acetic acid at room temperature, 28.9 mg 5-(4-sulfamoylphenyl)-2-furaldehyde (0.115 mmol) and 28.3 mg anhydrous NaOAc (0.345 mmol) were added. The resulting mixture was heated to 100 °C overnight, cooled to room temperature, diluted with $CHCl_3$ and water and filtered. The solid was dried under vacuum to give 46 mg compound 12 as a yellow solid (75%). ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) 5.26 (s, 2H), 7.32 (m, 2H), 7.44 (m, 3H), 7.50 (m, 2H), 7.55 (br. s, 1H), 7.76 (s, 1H), 7.98 (d, J = 8.8 Hz, 2H), 8.03 (d, J = 8.8 Hz, 2H).

Example 6: Compound 1

Compound 1 was prepared according to the method of Example 5. ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) 5.27 (s, 2 H), 7.32 (m, 5H), 7.42 (d, J = 3.7 Hz, 1H), 7.44 (s, 2H), 7.49 (d, J = 3.7 Hz, 1H), 7.75 (s, 1H), 7.98 (d, J = 8.8 Hz, 2H), 8.03 (d, J = 8.8 Hz, 2H).

Example 7: Compound 15

Compound 15 was prepared according to the method of Example 5. ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) 1.23 (m, 4H), 1.38 (m, 2H), 1.49 (m, 2H), 2.79 (td, J = 7.0, 5.7 Hz, 2H), 3.93 (t, J = 6.8 Hz, 2H), 5.27 (s, 2 H), 7.32 (m, 5H), 7.42 (d, J = 4.0 Hz, 1H), 7.50 (d, J = 4.0 Hz, 1H), 7.63 (t, J = 5.7 Hz, 1H), 7.75 (s, 1H), 7.95 (d, J = 8.8 Hz, 2H), 8.05 (d, J = 8.8 Hz, 2H).

Example 8: Compound 8

Compound 8 was prepared according to the method of Example 5. ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) 5.17 (s, 2H), 5.99 (s, 2H), 6.84 (dd, J = 7.9, 1.5 Hz, 1H), 6.87 (d, J = 7.9 Hz, 1H), 6.93 (d, J = 1.5 Hz, 1H), 7.42 (d, J = 3.7 Hz, 1H), 7.43 (s, 2H), 7.49 (d, J = 3.7 Hz, 1H), 7.74 (s, 1H), 7.98 (d, J = 8.8 Hz, 2H), 8.03 (d, J = 8.8 Hz, 2H).

Example 9: Compound 11

Compound 11 was prepared according to the method of Example 5. ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) 2.32 (s, 3H), 5.12 (s, 2H), 5.92 (s, 2H), 6.48 (s, 1H), 6.81 (s, 1H), 7.43 (m, 3H), 7.50 (d, J = 3.7 Hz, 1H), 7.75 (s, 1H), 7.99 (d, J = 8.8 Hz, 2H), 8.04 (d, J = 8.8 Hz, 2H).

Example 10: Compound 10

Compound 10 was prepared according to the method of Example 5. ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) 2.86 (s, 6H), 5.14 (s, 2H), 6.66 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 3.7 Hz, 1H), 7.43 (s, 2H), 7.48 (d, J = 3.7 Hz, 1H), 7.72 (s, 1H), 7.98 (d, J = 8.8 Hz, 2H), 8.02 (d, J = 8.8 Hz, 2H).

Example 11: Compound 7

Compound 7 was prepared according to the method of Example 5. ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) 1.86 (tt, J = 7.7, 7.3 Hz, 2H), 2.27 (t, J = 7.3 Hz, 2H), 2.69 (t, J = 7.7 Hz, 2H), 7.31 (d, J = 8.6 Hz, 2H), 7.38 (d, J = 8.6 Hz, 2H), 7.40 (s, 2H), 7.67 (d, J = 8.8 Hz, 2H), 7.72 (s, 1H), 7.90 (d, J = 8.8 Hz, 2H), 12.06 (br. s, 1H).

Example 12: Compound 9

Compound 9 was prepared according to the method of Example 5. ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) 3.08 (dd, J = 4.8, 4.2 Hz, 4H), 3.78 (dd, J = 4.8, 4.2 Hz, 4H), 7.31 (d, J = 8.8 Hz, 1H), 7.38 (dd, J = 8.8, 2.6 Hz, 1H), 7.40 (d, J = 4.0 Hz, 1H), 7.41 (d, J = 4.0 Hz, 1H), 7.57 (d, J = 2.6 Hz, 1H), 7.72 (s, 1H), 7.80 (d, J = 9.2 Hz, 2H), 7.83 (d, J = 9.2 Hz, 2H).

Example 13: Compound 6

Compound 6 was prepared according to the method of Example 5. ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) 2.24 (s, 3H), 2.47 (m, 4H), 3.23 (m, 4H), 7.05 (d, 9.2 Hz, 2H), 7.19 (d, J = 9.2 Hz, 2H), 7.39 (d, J = 3.7 Hz, 1H), 7.41 (d, J = 3.7 Hz, 1H), 7.67 (d, J = 8.8 Hz, 2H), 7.71 (s, 1H), 7.90 (d, J = 8.8 Hz, 2H).

Example 14: Compound 29

Compound 29 was prepared according to theescribed method of Example 5. ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) 3.24 (s, 3H), 3.45 (dd, J = 5.9, 4.0 Hz, 2H), 3.56 (dd, J = 5.9, 4.0 Hz, 2H), 3.68 (m, 2H), 3.74 (m, 2H), 4.17 (s, 2H), 4.45 (s, 4H), 7.22 (m, 3H), 7.40 (m, 3H), 7.51 (m, 3H), 7.66 (dd, J = 9.2, 2.6` Hz, 1H), 7.70 (s, 1H), 7.86 (d, J = 8.8 Hz, 2H), 8.07 (d, J = 2.6 Hz, 1H), 8.81 (d, J = 9.2 Hz, 1H).

Example 15: Compound 14

Compound 14 was prepared according to the method of Example 5. ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) 3.01 (q, J = 5.3 Hz, 2H), 3.75 (t, J = 5.3 Hz, 2H), 3.87 (t, J = 4.6 Hz, 2H), 4.30 (t, J = 4.6 Hz), 7.32 (d, J = 8.8 Hz, 1H), 7.40 (d, J = 4.0 Hz,1H), 7.42 (d, J = 4.0 Hz, 1H), 7.55 (dd, J = 8.8, 2.6 Hz, 1H), 7.71 (m, 2H), 7.81 (m, 4H).

Example 16: Compound 19

Compound 19 was prepared according to the method of Example 5. ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) 4.03 (s, 2H), 5.27 (s, 2H), 5.67 (br. s, 1H), 7.25 (d, J = 3.7 Hz, 1H), 7.26-7.34 (m, 5H), 7.40 (d, J = 3.7 Hz, 1H), 7.71 (s, 1H), 7.82 (d, J = 8.8 Hz, 2H), 7.91 (d, J = 8.8 Hz, 2H), 9.90 (s, 1H).

Example 17: Compound 22

Compound 22 was prepared according to the method of Example 5. ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) 2.33 (s, 3H), 3.80 (s, 2H), 5.12 (s, 2H), 5.93 (s, 2H), 6.46 (s, 1H), 6.81 (s, 1H), 7.27 (d, J = 3.7 Hz, 1H), 7.41 (d, J

= 3.7 Hz, 1H), 7.72 (s, 1H), 7.80 (d, J = 8.8 Hz, 2H), 7.88 (d, J = 8.8 Hz, 2H).

Example 18: Compound 23

Compound 23 was prepared according to the method of Example 5. ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) 5.19 (s, 2H), 6.68 (m, 1H), 6.72 (m, 1H), 6.75 (m, 1H), 7.13 (dd, J = 7.7, 8.0 Hz, 1H), 7.34 (br. s, 2H), 7.42 (d, J = 3.7 Hz, 1H), 7.47 (d, J = 3.7 Hz, 1H), 7.75 (s, 1H), 7.99 (d, J = 8.8 Hz, 2H), 8.03 (d, J = 8.8 Hz, 2H).

Example 19: Compound 26

Compound 26 was prepared according to the method of Example 5. ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) 5.27 (s, 2H), 7.28 (ddd, J = 6.2, 2.6, 1.6 Hz, 1H), 7.37-7.45 (m, 6 H), 7.49 (d, J = 4.0 Hz, 1H), 7.76 (s, 1H), 7.99 (d, J = 8.8 Hz, 2H), 8.04 (d, J = 8.8 Hz, 2H).

Example 20: Compound 27

Compound 27 was prepared according to the method of Example 5. ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) 5.23 (s, 2H), 7.15 (t, J - 7.7 Hz, 1 H), 7.33, m, 1H), 7.43 (d, J = 3.7 Hz, 1H), 7.44 (br. s, 2H), 7.49 (d, J = 3.7 Hz, 1 H), 7.67 (m, 1H), 7.73 (m, 1H), 7.78 (s, 1H), 7.98 (d, J = 8.8 Hz, 2H), 8.04 (d, J = 8.8 Hz, 2H).

Example 21: Compound 28

Compound 28 was prepared according to the method of Example 5. ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) 2.92 (s, 6H), 6.61 (dd, J = 7.7, 1.8 Hz, 1H), 6.72 (dd, J = 2.2, 1.8 Hz, 1H), 6.83 (dd, J = 8.4, 2.2 Hz, 1H), 7.33 (dd, J = 8.4, 7.7 Hz, 1H), 7.39 (d, J = 3.7 Hz, 1H), 7.41 (d, J = 3.7 Hz, 1H), 7.70 (s, 1H), 7.80 (d, J = 8.8 Hz, 2 H), 7.83, (d, J = 8.8 Hz, 2H).

Example 22: Compound 13

To a suspension of 26.6 mg *tert*-butyl *N*-[2-(4-5-[(3-benzyl-4-oxo-2-thioxo-1,3-thiazolan-5-ylidene)methyl]-2-furylanilino)-2-oxoethyl]carbamate

(0.0484 mmol, prepared according to previously described methods) in 0.24 ml dioxane at room temperature under nitrogen, 0.24 ml of a 4.0 M solution of HCl in dioxane (0.96 mmol) was added. The mixture was vigorously stirred at room temperature for 3 hours then was diluted with ether and filtered, washing with ether. The solid was dried under vacuum to give 22 mg compound 13·HCl as an orange powder (94%). ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) 3.83 (s, 2H), 5.27 (s, 2H), 7.27 (d, J = 3.9 Hz, 1H), 7.33 (m, 5H), 7.41 (d, J = 3.9 Hz, 1H), 7.72 (s, 1H), 7.81 (d, J = 8.8 Hz, 2H), 7.87 (d, J = 8.8 Hz, 2H), 8.15 (br. s, 3H), 10.81 (br. s, 1H).

Example 23: Compound 21

Step 1: To a solution/suspension of 0.25 g 3-aminorhodanine (1.7 mmol) in 6.8 ml dichloromethane was added 0.35 ml triethylamine (2.6 mmol). The mixture was chilled in an ice bath and treated with 0.24 ml benzoyl chloride (2.0 mmol). After 15 minutes, the mixture was diluted with dichloromethane and washed with 2N hydrochloric acid, saturated aqueous $NaHCO_3$, 2N hydrochloric acid, water and brine. The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with 3:1 hexanes:EtOAc to give 75 mg 3-benzamidorhodanine (17%).

Step 2: Compound 21 was prepared according to the methods described above from 3-benzamidorhodanine and the appropriate starting materials. ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) 7.43 (br. s, 2H), 7.49 (br. s, 1H), 7.52 (br. s, 1H), 7.59 (t, J = 7.7 Hz, 2H), 7.69 (t, J = 7.7 Hz, 1H), 7.87 (s, 1H), 8.00 (m, 4H), 8.07 (d, J = 8.4 Hz, 2H), 11.73 (br. s, 1H).

Example 24: Compound 24

Step 1: To a solution of 0.25 g 2-(5-[5-(4-bromophenyl)-2-furyl]methylidene-4-oxo-2-thioxo-1,3-thiazolan-3-yl)acetic acid (0. 59 mmol, prepared according to previously described methods) in 0.5 ml DMF was added 0.24 g O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (0.63 mmol) and 0.11 ml N,N-diisopropylethylamine

(0.65 mmol) at room temperature. After 30 minutes, 0.25 g piperazine (3.0 mmol) was added and the mixture was stirred overnight. The reaction mixture was diluted with water and diethyl ether. The solid was filtered to give 0.26 g compound 24 (90%). ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) 3.03 (br. s, 2H), 3.13 (br. s, 2H), 3.71 (br. s, 2H), 3.89 (br. s, 2H), 5.03 (s, 2H), 7.42 (s, 2H), 7.75 (s, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 8.4 Hz, 2H).

Example 25: Compound 25

Step 1: To a solution of 46 mg t-butoxycarbonylglycine (0.26 mmol) in 1 ml DMF at room temperature, 98 mg O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluoro-phosphate (0.26 mmol) and 50 ml N,N-diisopropylethylamine (0.28 mmol) were added. The solution was stirred 30 minutes and then 0.128 g compound 24 (0.26 mmol) was added. The resulting mixture was stirred overnight, diluted with water and filtered. The filter cake was washed further with water and diethyl ether. The solid was dried over P_2O_5 to give 0.13g *tert*-butyl *N*-(2-4-[2-(5-[5-(4-bromophenyl)-2-furyl]methylidene-4-oxo-2-thioxo-1,3-thiazolan-3-yl)acetyl]piperazino-2-oxoethyl)carbamate (76%).

Step 2: A suspension of 0.13g *tert*-butyl *N*-(2-4-[2-(5-[5-(4-bromophenyl)-2-furyl]methylidene-4-oxo-2-thioxo-1,3-thiazolan-3-yl)acetyl]piperazino-2-oxoethyl)carbamate (0.20 mmol) in 0.80 ml 1,4-dioxane was treated with 0.80 ml 4M HCl in 1,4-dioxane. The suspension was stirred overnight. The reaction mixture was diluted with diethyl ether and filtrated. The solid was dried under vacuum to give 0.12 g compound 25 (100%). ^{1}H NMR (400 MHz, CD_3OD + trace $CD_3SO_2CD_3$) 3.49 (m, 2H), 3.67 (m, 4H), 3.74 (m, 2H), 3.98 (s, 2H), 5.08 (s, 2H), 7.16 (d, 3.7 Hz, 1H), 7.21 (d, J = 3.7 Hz, 1H), 7.63 (s, 1H), 7.70 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 8.8 Hz, 2H).

Example 26: Compound 20

Step 1: A suspension of 0.50 g -alanine (5.6 mmol) in 10 ml 2-propanol, 3 ml water and 1.7 ml triethylamine (12.3 mmol) were heated to reflux to give a cloudy solution. The solution was cooled and 0.36 ml carbon

disulfide (6.2 mmol) was added. The resulting mixture was stirred overnight at room temperature. The clear yellow solution was treated with 0.72g sodium chloroacetate (6.2 mmol) and refluxed for 25 minutes. The hot mixture was acidified with 2.5 ml glacial acetic acid and heated for an additional 10 minutes. The mixture was cooled to room temperature and the 2-propanol was removed under reduced pressure. After stirring 2 hours at room temperature, the solution was chilled in an ice bath and diluted further with 3 ml water. The precipitate, which formed over 0.5 hours, was filtered and washed with water. The solid was dried under vacuum to give 0.51 g 3-(2-carboxyethyl)rhodanine as a yellow solid (51%).

Step 2: 3-(5-[5-(4-Bromophenyl)-2-furyl]methylidene-4-oxo-2-thioxo-1,3-thiazolan-3-yl)propanoic acid was prepared according to the methods described above from 3-(2-carboxyethyl)rhodanine and the approriate starting materials.

Step 3: To a solution of 45 mg 3-(5-[5-(4-bromophenyl)-2-furyl]methylidene-4-oxo-2-thioxo-1,3-thiazolan-3-yl)propanoic acid (0.10 mmol) in 2.0 ml DMF was added 19 ml N,N-diisopropylethylamine (0.11 mmol) and 42 mg O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (0.11 mmol). After 1.5 hours at room temperature, 12 ml 1-methylpiperazine (0.11 mmol) was added and the mixture was stirred overnight. The solution was treated with 1 ml 2N hydrochloric acid and concentrated to dryness under reduced pressure. The residue was brought up in a minimum amount of methanol and the precipitated with diethyl ether. The solid was filtered and dried under vacuum to give 37 mg compound 20 (66%). ^{1}H NMR (400 MHz, CD_3OD + trace $CD_3SO_2CD_3$) 2.69 (br. s, 4H), 2.89 (dd, J = 7.7, 7.3 Hz, 2H), 2.92 (s, 3H), 3.21 (v. br. s, 2H), 3.34 (v. br. s, 2H), 4.40 (dd, J = 7.7, 7.3 Hz, 2H), 7.14 (d, J = 4.0 Hz, 1H), 7.18 (d, J = 4.0 Hz, 1H), 7.59 (s, 1H), 7.68 (d, J = 8.8 Hz, 2H), 7.76 (d, J = 8.8 Hz, 2H).

Compounds of Scheme 2

Example 27: Compound 2

Step 1: To a solution of 556 mg maleic anhydride (5.67 mmol) in 6 ml DMF at room temperature under nitrogen, 1.01 g 4-morpholinoaniline (5.67 mmol) was added. The resulting mixture was stirred at room temperature for 1 hour then concentrated under vacuum to give 1.55 g orange solid (99%). This material was used without further purification. ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) 3.07 (t, J = 4.8 Hz, 4H), 3.73 (t, J = 4.6 Hz, 4H), 6.29 (d, J = 12.3 Hz, 1H), 6.47 (d, J = 12.3 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 10.39 (br. s, 1H).

Step 2: To a flask containing 1.55g anilide (5.61 mmol) at room temperature under nitrogen, 2.6 ml acetic anhydride and 230 mg anhydrous sodium acetate (2.81 mmol) were added. The resulting mixture was heated to 100 °C for 30 minutes, cooled to room temperature and poured onto ice. The mixture was diluted with water and extracted twice with EtOAc. The organic phases were combined, washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated under vacuum and the residue was filtered though silica gel eluting with 2:1 $CHCl_3$:EtOAc to give 900 mg bright orange solid. This material was recrystallized to yield 540 mg N-(4-morpholinophenyl)maleimide as a bright orange solid (37%). ^{1}H NMR (400 MHz, $CDCl_3$) 3.18 (t, J = 4.8 Hz, 4H), 3.86 (t, J = 4.8 Hz, 4H), 6.82 (s, 2H), 6.96 (d, J = 9.0 Hz, 2H), 7.20 (d, J = 9.0 Hz, 2H).

Step 3: To a solution of 529 mg N-(4-morpholinophenyl)maleimide (2.05 mmol) in 8.2 ml acetic acid at room temperature under nitrogen, 591 mg triphenylphosphine (2.26 mmol) was added. The resulting mixture was heated to 100 °C for 1 hour, cooled to room temperature and 30 ml ether was added. The ether was decanted from the product which had oiled out. An additional 20 ml ether was added and the product solidified. The solvent was again decanted and the remaining solid was treated with hot acetone, cooled to room temperature and filtered to give 710 mg lavender

solid (67 %). ^{1}H NMR (400 MHz, $CDCl_3$) 3.10 (t, J = 4.8 Hz, 4H), 3.13 (s, 2H), 3.83 (t, J = 4.8 Hz, 4H), 6.93 (d, J = 9.0 Hz, 2H), 7.34 (d, J = 9.0 Hz, 2H), 7.52 (m, 6H), 7.63 (m, 9H).

Step 4: To a solution of 75 mg ylide (0.14 m mol) in 0.6 ml CH_3OH at room temperature under nitrogen, 30 mg 5-(4-chlorophenyl)-2-furaldehyde was added. The resulting mixture was heated to 70 °C for 10 minutes, cooled to room temperature and filtered. The solid was dried under vacuum to give 56 mg compound 2 as a yellow solid (86%). ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) 3.17 (t, J = 4.8 Hz, 4H), 3.77 (t, J = 4.8 Hz, 4H), 3.87 (d, J = 2.2 Hz, 2H), 7.04 (d, J = 9.2 Hz, 2H), 7.16 (d, J = 3.7 Hz, 1H), 7.20 (d, J = 9.2 Hz, 2H), 7.27 (d, J = 3.7 Hz, 1H), 7.40 (t, J = 2.2 Hz, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.86 (d, J = 8.8 Hz, 2H).

Example 28: Compound 3

Compound 3 was prepared according to the method of Example 27. ^{1}H NMR (400 MHz, $CDCl_3$) 3.20 (t, J = 4.8 Hz, 4H), 3.73 (d, J = 2.2 Hz, 2H), 3.85 (t, J = 4.8 Hz, 4H), 6.87 (d, J = 4 Hz, 1H), 6.97 (m, 3H), 7.25 (d, J = 9.2 Hz, 2H), 7.47 (t, J = 2.2 Hz, 1H), 7.90 (s, 2H), 8.00 (s, 1H).

Example 29: Compound 16

Compound 16 was prepared according to the method of Example 27. ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) 2.31 (s, 3H), 3.88 (d, J = 2.2 Hz, 2H), 4.59 (s, 2H), 5.93 (s, 2H), 6.73 (s, 1H), 6.77 (s, 1H), 7.18 (d, J = 3.6 Hz, 1H), 7.38 (m, 4H), 7.92 (d, J = 8.8 Hz, 2H), 8.00 (d, J = 8.8 Hz, 2H).

Example 30: Compound 17

Compound 17 was prepared according to the method of Example 27. ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) 2.32 (s, 3H), 3.85 (d, J = 2.2 Hz, 2H), 4.59 (s, 2H), 5.93 (s, 2H), 6.74 (s, 1H), 6.77 (s, 1H), 7.41 (m, 1H), 7.50 (m, 2H), 7.55 (t, J = 2.2 Hz, 1H), 7.73-7.82 (m, 6H).

Example 31: Compound 18

Compound 18 was prepared according to the method of Example 27. ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) 1.97 (m, 4H), 2.30 (s, 3H), 3.30 (m, 4H), 3.69 (d, J = 2.2 Hz, 1H), 4.55 (s, 2H), 5.92 (s, 2H), 6.61 (d, J = 8.8 Hz, 2H), 6.69 (s, 1H), 6.76 (s, 1H), 7.38 (t, J = 2.2 Hz, 1H), 7.47 (d, J = 8.8 Hz, 2H).

Compounds of Scheme 3

Example 32: Compound 5

Step 1: To a suspension of 2.19 g zinc dust (33.5 mmol) in 11 ml glacial acetic acid at reflux under nitrogen, 0.90 g 3-benzylrhodanine (4.0 mmol) was added in three equal portions spaced 1 hour apart. The mixture was stirred at reflux for 1 additional hour after the last addition and then was cooled to room temperature. Celite and $CHCl_3$ was added and the reaction mixture was filtered through Celite. The filtrate was concentrated under vacuum and the residue was purified by silica gel chromatography, eluting with 9:1 increasing to 17:3 hexanes:ethyl acetate to yield 260 mg 3-benzylthiazolan-4-one as a light yellow oil (33%).

Step 2: To a solution of 1.24g 5-bromo-2-furoic acid (6.5 mmol) in 22 ml DMF at room temperature under nitrogen, 0.87 g phenylboric acid (7.1 mmol) and a solution of 4.52 g K_3PO_4 (21.3 mmol) in 11 ml H_2O were added. The system was deoxygenated by transferring from vacuum to nitrogen feed five times and then a catalytic amount of $Pd(PPh_3)_2Cl_2$ was added. The system was deoxygenated as before and then the reaction mixture was heated to 80 °C overnight. The mixture was cooled to room temperature and filtered through Celite, washing with ethyl acetate and 2N NaOH. The aqueous phase was acidified to pH 1 with 2N HCl and extracted three times with ethyl acetate. The combined organic phases were washed with brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated under vacuum to yield 1.57 g 5-phenyl-2-furoic acid (contains DMF) as a brown oily solid. The material was used without purification.

Step 3: To a solution of 1.57 g crude 5-phenyl-2-furoic acid (6.5 mmol theoretical) in 22 ml DMF at room temperature under nitrogen, 0.61 ml iodomethane (9.75 mmol) and 0.32 g Cs_2CO_3 (9.75 mmol) were added sequentially. The resulting mixture was stirred at room temperature for 2 hours, was diluted with a 3:1 mixture of hexanes:ethyl acetate and washed with H_2O four times and once with brine. The organic phase was dried over $MgSO_4$ and filtered and the filtrate was concentrated under vacuum to give 1.67 g light yellow oil. This material was filtered through silica gel, eluting with hexanes, increasing to 19:1 and finally 9:1 hexanes:ethyl acetate to yield 1.21 g methyl 5-phenyl-2-furoate as a colorless oil which solidified on standing (92 % for 2 steps).

Step 4: To a solution of 91 mg 3-benzylthiazolan-4-one (0.47 mmol) and 96 mg methyl 5-phenyl-2-furoate (0.47 mmol) in 1.9 ml THF at 0 °C under nitrogen, 1.9 ml of a 0.50M solution of potassium hexamethyldisilazide in toluene (0.95 mmol) was added dropwise by syringe. The resulting mixture was allowed to warm to room temperature and was stirred for 1 hour. The reaction was quenched with 2N HCl and diluted with ethyl acetate. The organic phase was washed twice with H_2O and once with brine, dired over MgSO4 and then filtered. The filtrate was concentrated under vacuum to give 208 mg burnt orange solid. This material was recrystallized from hexanes/ethyl acetate to give 112 mg 3-benzyl-5-(5-phenyl-2-furoyl)thiazolan-4-one as yellow-orange needle crystals (65%).

Step 5: To a suspension of 86 mg 3-benzyl-5-(5-phenyl-2-furoyl)thiazolan-4-one (0.24 mmol) in 0.96 ml absolute ethanol at room temperature under nitrogen, 10 mg $NaBH_4$ (0.24 mmol) was added. The mixture was stirred at room temperature for 2 hours, was diluted with CH_2Cl_2 and washed with a 2:1 mixture of H_2O:saturated aqueous NH_4Cl, H_2O and brine. The organic phase was dried and filtered and the filtrate was concentrated under vacuum to give 81 mg 3-benzyl-5-[hydroxy(5-phenyl-2-furyl)methyl]-1,3-thiazolan-4-one as a light yellow solid (mixture of distereomers). This material was used without purification.

Step 6: To a solution of 81 mg crude 3-benzyl-5-[hydroxy(5-phenyl-2-furyl)methyl]-1,3-thiazolan-4-one (0.22 mmol) in 2.4 ml benzene at room temperature under nitrogen, 46 mg p-TsOH•H_2O (0.24 mmol) was added. The resulting mixture was brought to reflux for 30 minutes, then was cooled to room temperature and concentrated under vacuum. The reisdue was taken up in ethyl acetate and washed twice with saturated $NaHCO_3$ and brine. The organic phase was dried over MgSO4 and filtered and the filtrate was concentrated under vacuum to give 78 mg of a light yellow solid. This material was purified by silica gel chromatography, eluting with 19:1 hexanes:ethyl acetate increasing to 4:1 hexanes:ethyl acetate to yield 71 mg light yellow solid. Recrystallization of this material from hexanes/ethyl acetate gave 55 mg compound 5 as light yellow needle crystals (66% for 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) 4.48 (s, 2H), 4.74 (s, 2H), 6.64 (d, J = 3.7 Hz, 1H), 6.78 (d, J = 3.7 Hz, 1H), 7.26-7.43 (m, 9H), 7.74 (m, 2H).

Example 33: Compound 4

Compound 4 was prepared by the methods of Example 32. ^{1}H NMR (400 MHz, $CDCl_3$) 3.18 (td, J = 6.6, 2.6 Hz, 2H), 3.42 (t, J = 6.6 Hz, 2H), 4.62 (s, 2H), 6.61 (d, J = 3.7 Hz, 1H), 6.75 (d, J = 3.7 Hz, 1H), 7.22 (t, J = 2.6 Hz, 1H), 7.26-7.37 (m, 6H), 7.39 (t, J = 7.7 Hz, 2H), 7.66 (d, J = 7.7 Hz, 2H).

Compound of Scheme 4

Example 34: Compound 30

Step 1: A suspension of 38 mg 3-benzylhydantoin (0.20 mmol) in 0.80 ml 2:1 methanol:water was treated with 30 ml triethylamine (0.22 mmol). The reaction vessel was sealed and heated in an oil bath at 110 °C overnight. The mixture was cooled, diluted with water and ethyl acetate. The organic layer was concentrated, and the residue was recrystallized from acetonitrile. The solid was filtered and dried to give 65.8 mg *tert*-butyl

N-[2-(4-5-[(1-benzyl-2,5-dioxotetrahydro-4*H*-imidazol-4-ylidene)methyl]-2-furylanilino)-2-oxoethyl]carbamate (64%).

Step 2: To a suspension of 25 mg *tert*-butyl *N*-[2-(4-5-[(1-benzyl-2,5-dioxotetrahydro-4*H*-imidazol-4-ylidene)methyl]-2-furylanilino)-2-oxoethyl]carbamate (0.048 mmol) in 0.20 ml 1,4-dioxane, 0.20 ml 4M-HCl in 1,4-dioxane was added at room temperature. The mixture was stirred overnight, then diluted with diethyl ether and filtered. The solid was dried under vacuum to give 18.8 mg compound 30 (94%). ^{1}H NMR (400 MHz, $CD_3SO_2CD_3$) 3.80 (br. s, 2H), 4.69 (s, 2H), 6.53 (s, 1H), 7.08 (d, J = 3.6 Hz, 1H), 7.14 (d, J = 3.6 Hz, 1H), 7.32 (m, 5H), 7.69 (d, J = 8.8 Hz, 2H), 7.93 (d, J = 8.8 Hz, 2H), 8.15 (br. s, 1H), 10.68 (br. s, 1H).

The present invention is also illustrated by the biological data that is generated pursuant to the hereinafter described protocols:

Biological Assays

[^{125}I]VEGF binding to *flt*-IgG fusion proteins:

The seven loop ectodomain of the human *flt* receptor was cloned into a vector containing the heavy chains of the mouse IgG2a for use in a baculovirus expression system. Insect cells (*sf*-21) were grown on T-175 flasks (Falcon) in SFM-900 II serum-free growth media for 2-3 days following infection with virus. Immulon-4 plates were coated overnight at 4°C with 100-ng/well of goat-antimouse IgG2a specific antibodies diluted in PBS. Wells were washed 3 x PBS containing 0.05% Tween-20 then 3 x PBS. Wells were blocked with 1% BSA in PBS for 3 hours at room temperature. Wells were again washed 3 x PBS/Tween-20 then 3 x PBS. Conditioned media from infected cells was added to the wells and allowed to incubate overnight at 4°C. The wells were then washed 3 x PBS/Tween-20 then 3 x PBS. Antagonists were added 30 min prior to the adittion of 2 ng/ml [^{125}I]VEGF (Biotechnology Technologies, Inc.) in a total volume of 0.10 ml/well. Nonspecific binding was determined as the amount of [^{125}I]VEGF bound in the presence of 200 ng/ml VEGF. After 1.5

hours at room temperature, the wells were washed with 3 x 200-µl ice-cold PBS. The wells were separated and transferred to polypropylene tubes and counted in the counter for 1 minute.

[^{125}I]VEGF binding to *KDR*-IgG fusion proteins:

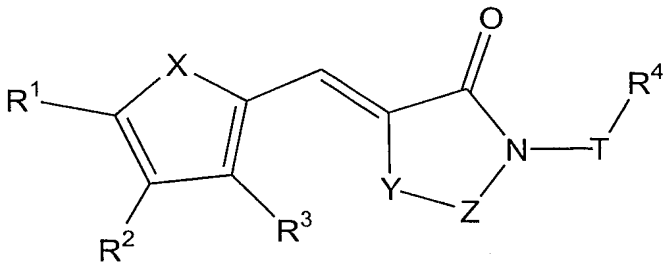
The seven loop ectodomain of the human *KDR* receptor was cloned into a vector containing the heavy chains of the mouse IgG2a for use in a baculovirus expression system. Insect cells (*sf*-21) were grown on T-175 flasks (Falcon) in SFM-900 II serum-free growth media for 2-3 days following infection with virus. Immulon-4 plates were coated overnight at 4°C with 100-ng/well of goat-antimouse IgG2a specific antibodies diluted in PBS. Wells were washed 3 x PBS containing 0.05% Tween-20 then 3 x PBS. Wells were blocked with 1% BSA in PBS for 3 hours at room temperature. Wells were again washed 3 x PBS/Tween-20 then 3 x PBS. Conditioned media from infected cells was added to the wells and allowed to incubate overnight at 4°C. The wells were then washed 3 x PBS/Tween-20 then 3 x PBS. Antagonists were added 30 min prior to the addition of 2 ng/ml [^{125}I]VEGF (Biotechnology Technologies, Inc.) in a total volume of 0.10 ml/well. Nonspecific binding was determined as the amount of [^{125}I]VEGF bound in the presence of 200 ng/ml VEGF. After 1.5 hours at room temperature, the wells were washed with 3 x 200-µl ice-cold PBS. The wells were separated and transferred to polypropylene tubes and counted in the counter for 1 minute.

Inhibition of VEGF-stimulated HUVEC growth:

HUVECs were plated at 12500 cells/cm^2 on gelatin coated 48-well plates (Falcon). The following day, the cells were placed in a defined media of M199/15% FBS/10 µM thymidine and 10 ng/ml rh VEFR165 with or without various concentrations of antagonist. After four days in culture, the cells were removed from the well with 100-µl of 0.5% trypsin and counted with a Coulter cell counter. Data is presented as the number of cells/cm^2.

WHAT IS CLAIMED:

1. A compound of the formula:



1

where:

X is O, S, or $-CR^5=CR^6-$;
Y is O, S, NR^7, or CH_2,
Z is CH_2, C=O, or C=S,
T is $(CH_2)_n$, NR^8, or $N(R^9)CO$;
R^1, R^2, R^3, R^5, and R^6 are independently selected from the group consisting of hydrogen, heteroatoms, substituted or unsubstituted cycloalkyl, aryl, and heterocyclyl groups;
R^4 is selected from the list consisting of hydrogen, substituted or unsubstituted alkyl, cycloalkyl, aryl, heterocyclyl, or carboxamide groups;
R^7 is hydrogen or a substituted or unsubstituted alkyl group;
R^8 and R^9 are independently selected from the group consisting of hydrogen, substituted or unsubstituted alkyl, cycloalkyl, aryl, and heterocyclyl groups. R^4 and R^8 may also form part of a ring; and
n is 0-6;
and the pharmaceutically acceptable salts and prodrugs thereof.

2. A compound of claim 1 where

X is O;

when Y is S, Z is C=S;
when Y is NH, Z is C=O; and
when Y is CH_2, Z is C=O;
T is $(CH_2)_n$;
n is 0-3;
R^1 is independently selected from the group consisting of substituted or unsubstituted aryl, and heterocyclyl groups;
R^2 and R^3 are hydrogen; and
R^4 is selected from the group consisting of substituted or unsubstituted aryl, heterocyclyl, and carboxamide groups;
and the pharmaceutically acceptable salts and prodrugs thereof.

3. A compound of claim 1 selected from the group consisting of
4-{5-[(3-benzyl-4-oxo-2-thioxo-1,3-thiazolan-5-ylidene)methyl]-2-furyl}benzenesulfonamide,
3-{[5-(4-chlorophenyl)-2-furyl]methylidene}-1-(4-morpholinophenyl)dihydro-1H-pyrrole-2,5-dione,
1-(4-morpholinophenyl)-3-({5-[2-nitro-4-(trifluoromethyl)phenyl]-2-furyl}methylidene)dihydro-1H-pyrrole-2,5-dione,
1-benzyl-3-[(5-phenyl-2-furyl)methylidene]-2-pyrrolidinone,
3-benzyl-5-[(5-phenyl-2-furyl)methylidene]-1,3-thiazolan-4-one,
5-{[5-(4-chlorophenyl)-2-furyl]methylidene}-3-[4-(4-ethylpiperazino)phenyl]-2-thioxo-1,3-thiazolan-4-one,
4-[4-(5-{[5-(4-chlorophenyl)-2-furyl]methylidene}-4-oxo-2-thioxo-1,3-thiazolan-3-yl)phenyl]butanoicacid,
4-(5-{[3-(1,3-benzodioxol-5-ylmethyl)-4-oxo-2-thioxo-1,3-thiazolan-5-ylidene]methyl}-2-furyl)benzenesulfonamide,
5-{ [5-(4-bromophenyl)-2-furyl]methylidene}-3-(3-chloro-4-morpholinophenyl)-2-thioxo-1,3-thiazolan-4-one,
4-[5-({3-[4-(dimethylamino)benzyl]-4-oxo-2-thioxo-1,3-thiazolan-5-ylidene}methyl)-2-furyl]benzenesulfonamide,
4-[5-({3-[(6-methyl-1,3-benzodioxol-5-yl)methyl]-4-oxo-2-thioxo-1,3-thiazolan-5-ylidene}methyl)-2-furyl]benzenesulfonamide,

4-(5-{[3-(3-bromobenzyl)-4-oxo-2-thioxo-1,3-thiazolan-5-ylidene]methyl}-2-furyl)benzenesulfonamide,

2-amino-N-(4-{5-[(3-benzyl-4-oxo-2-thioxo-1,3-thiazolan-5-ylidene)methyl]-2-furyl}phenyl)acetamide,

2-[2-(2-aminoethoxy)ethoxy]-5-(5-{[5-(4-bromophenyl)-2-furyl]methylidene}-4-oxo-2-thioxo-1,3-thiazolan-3-yl)benzoic acid,

4-{5-[(3-benzyl-4-oxo-2-thioxo-1,3-thiazolan-5-ylidene)methyl]-2-furyl}-N-(6-hydroxyhexyl)benzenesulfonamide,

4-[5-({1-[(6-methyl-1,3-benzodioxol-5-yl)methyl]-2,5-dioxo-3-pyrrolidinylidene}methyl)-2-furyl]benzenesulfonamide,

3-[[1,1'-biphenyl]-4-ylmethylidene]-1-[(6-methyl-1,3-benzodioxol-5-yl)methyl]dihydro-1H-pyrrole-2,5-dione,

1-[(6-methyl-1,3-benzodioxol-5-yl)methyl]-3-{[4-(1-pyrrolidinyl)phenyl]methylidene}dihydro-1H-pyrrole-2,5-dione,

N-(4-{5-[(3-benzyl-4-oxo-2-thioxo-1,3-thiazolan-5-ylidene)methyl]-2-furyl}phenyl)-2-hydroxyacetamide,

5-{[5-(4-bromophenyl)-2-furyl]methylidene}-3-[3-(4-methylpiperazino)-3-oxopropyl]-2-thioxo-1,3-thiazolan-4-one,

N-(5-{[5-(4-bromophenyl)-2-furyl]methylidene}-4-oxo-2-thioxo-1,3-thiazolan-3-yl)benzamide,

2-amino-N-{4-[5-({3-[(6-methyl-1,3-benzodioxol-5-yl)methyl]-4-oxo-2-thioxo-1,3-thiazolan-5-ylidene}methyl)-2-furyl]phenyl}acetamide,

4-(5-{[3-(3-hydroxybenzyl)-4-oxo-2-thioxo-1,3-thiazolan-5-ylidene]methyl}-2-furyl)benzenesulfonamide,

5-{[5-(4-bromophenyl)-2-furyl]methylidene}-3-(2-oxo-2-piperazinoethyl)-2-thioxo-1,3-thiazolan-4-one,

3-{2-[4-(2-aminoacetyl)piperazino]-2-oxoethyl}-5-{[5-(4-bromophenyl)-2-furyl]methylidene}-2-thioxo-1,3-thiazolan-4-one,

4-(5-{[3-(3-chlorobenzyl)-4-oxo-2-thioxo-1,3-thiazolan-5-ylidene]methyl}-2-furyl)benzenesulfonamide,

4-(5-{[3-(3-iodobenzyl)-4-oxo-2-thioxo-1,3-thiazolan-5-ylidene]methyl}-2-furyl)benzenesulfonamide,

5-{[5-(4-bromophenyl)-2-furyl]methylidene}-3-[3-(dimethylamino)phenyl]-2-thioxo-1,3-thiazolan-4-one,

5-{5-[(5-{4-[2-(3-cyanophenoxy)ethoxy]phenyl}-2-furyl)methylidene]-4-oxo-2-thioxo-1,3-thiazolan-3-yl}-2-({2-[2-(2-methoxyethoxy)ethoxy]acetyl}amino)benzoic acid,
2-amino-N-(4-{5-[(1-benzyl-2,5-dioxotetrahydro-4H-imidazol-4-ylidene)methyl]-2-furyl}phenyl)acetamide,
5-(5-{5-(4-bromophenyl)-2-furyl]methylidene}-4-oxo-2-thioxo-1,3-thiazolan-3-yl)-2-(2-{2-[(tert-butoxycarbonyl)amino]ethoxy}ethoxy)benzoic acid,
3-benzyl-5-({5-[4-(methoxymethoxy)phenyl]-2-furyl}methylidene)-2-thioxo-1,3-thiazolan-4-one,
2-{[2-(5-{[5-(4-bromophenyl)-2-furyl]methylidene}-4-oxo-2-thioxo-1,3-thiazolan-3-yl)acetyl]amino}acetic acid,
(2S)-5-{[amino(imino)methyl]amino}-2-{[2-(5-{[5-(4-bromophenyl)-2-furyl]methylidene}-4-oxo-2-thioxo-1,3-thiazolan-3-yl)acetyl]amino}pentanoic acid,
4-[5-({3-[(6-nitro-1,3-benzodioxol-5-yl)methyl]-4-oxo-2-thioxo-1,3-thiazolan-5-ylidene}methyl)-2-furyl]benzenesulfonamide,
2-(acetylamino)-5-(5-{[5-(3-hydroxyphenyl)-2-furyl]methylidene}-4-oxo-2-thioxo-1,3-thiazolan-3-yl)benzoic acid, and
3-benzyl-5-{[5-(3-hydroxyphenyl)-2-furyl]methylidene}-2-thioxo-1,3-thiazolan-4-one and the pharmaceutically acceptable salts and prodrugs thereof.

4. A pharmaceutical composition comprising at least one compound of formula 1 and a pharmaceutically acceptable carrier.

5. A method of inhibiting cellular proliferation by administering a therapeutically effective amount of a compound of formula 1 to a host in need of such treatment.